BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	Matthew J. During	
Application No.:	10/776,780-Conf. #3635	Group Art Unit: 1632
Filed:	February 10, 2004	Examiner: Anne Marie Falk
Entitled:	**Method for Modifying Target Receptor Function Associated With Neurological Disorders**	
Docket No.:	106604-7	

Certificate of Transmission

I hereby certify that this correspondence is being electronically transmitted via EFS-Web to the United States Patent and Trademark Office on the date set forth below.

November 10, 2010	Electronic Signature: /Thomas J. Engellenner/
Date	Thomas J. Engellenner, Reg. No: 28,711 Attorney for Applicant(s)

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-14

APPEAL BRIEF PURSUANT TO 37 C.F.R. § 41.37

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is Auckland Technology Enabling Corporation Limited of Wellington, New Zealand, which derives its rights in this application by virtue of an assignment of the application by the inventor to Auckland Technology Enabling Corporation Limited as recorded at Reel 018020, Frame 0526.

II. RELATED APPEALS AND INTERFERENCES

None.

III. STATUS OF CLAIMS

Claims 1-2, 10-12 and 20-28 are pending in the application. Claims 3-9 and 13-19 have been canceled. As of the Advisory Action mailed August 30, 2010, claims 1-2 and 10 are allowed and claims 11-12 and 20-28 stand rejected under 35 U.S.C. §112, first paragraph, as failing to enable one skilled in the art to make or use the invention as described by the claims.

More specifically, with the August 30, 2010, Advisory Action, the Examiner rejected claims 11-12 and 20-28 under 35 U.S.C. §112, first paragraph, as the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with the claims.

Accordingly, Appellant respectfully requests reconsideration of claims 11-12 and 20-28.

IV. STATUS OF AMENDMENTS

Subsequent to the Final Office Action mailed on December 10, 2009, Appellant submitted amendments and a response on June 10, 2010 to the Final Office Action. An Advisory Action issued on August 31, 2010 in response to the Appellant's remarks. The Examiner entered the amendments to claims 2, 11, and 12. The Examiner withdrew the rejection to claim 2 and maintained the rejection to claims 11-12 and 20-28 of the Final Office Action. No additional amendments have been proposed.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is directed to compositions and methods of using an N-methyl-D-aspartate (NMDA) receptor-1 antigen that elicits an immune response in a subject to produce NMDA receptor-1 antibodies that inhibit NMDA activity.

Allowed independent claim 1 recites a composition to inhibit N-methyl-D-aspartate activity comprising an adeno-associated virus vector comprising a nucleic acid sequence encoding for an N-methyl-D-aspartate (NMDA) receptor-1 antigen operably linked to a promoter and capable of being expressed in a subject to elicit production of NMDA receptor-1 antibodies that inhibit NMDA activity, and a pharmaceutically-acceptable carrier. Claim 2, which depends from claim 1 and is also allowed, recites a composition that elicits antibodies that bind to NMDA receptor in the central nervous system. Claims 10, which also depends from claim 1 and is likewise allowed, recites compositions prepared for oral administration. [Published application at paragraphs [0009], [0013], [0016], [0018], [0026], [0029], [0123]-[0127] and [0138].]

Independent claim 11 recites a method comprising the step of administering an adeno-associated viral (AAV) vector comprising a nucleic acid sequence encoding for an N-methyl-D-aspartate (NMDA) receptor-1 antigen operably linked to a promoter and capable of being expressed in a mammalian subject to elicit production of NMDA receptor-1 antibodies, and a pharmaceutically-acceptable carrier to a subject prior to a neuronal insult, whereby the produced NMDA receptor-1 antibodies are capable of passing across a blood-brain barrier into a central nervous system following the neuronal insult to inhibit NMDA activity. [Published application at paragraphs [0007], [0009], [0013]-[0014], [0016] and [0018].]

Independent claim 12 recites a method administering a composition to a mammalian subject to inhibit N-methyl-D-aspartate activity comprising a composition comprising a nucleic acid sequence encoding for an N-methyl-D-aspartate (NMDA) receptor-1 antigen, and a pharmaceutically-acceptable carrier prior to a neuronal insult, wherein the antigen elicits the production of NMDA receptor-1 antibodies in a circulatory system of the subject which bind to an NMDA receptor-1 in the central nervous system to ameliorate epilepsy or stroke in the mammalian subject. [Published application at paragraphs [0007], [0009], [0014], [0016] and [0018].]

Appellant's other dependent claims each recite more particular methods that depend, directly or indirectly on claim 12. Claims 20-23 recite methods using particular vectors. Claims 24-28 recite particular modes of administration. [Published application at paragraphs [0013], [0026], [0029], [0123]-[0127] and [0138].]

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether the Examiner improperly rejected claims 11-12 and 20-28 pursuant to 35 U.S.C. §112, first paragraph, as failing to enable one skilled in the art to make or use the invention as described by the claims.

VII. ARGUMENT

The Examiner improperly rejected claims 11-12 and 20-28 pursuant to 35 U.S.C. §112, first paragraph, as failing to enable one skilled in the art to make or use the invention as described by the claims.

1. The Examiner's Rejections

The Examiner rejects claims 11-12 and 20-28 under 35 U.S.C. §112, first paragraph, as failing to enable one skilled in the art to make or use the invention as described by the claims. Specifically, the Examiner states that:

> "the specification, while being enabling for (i) a composition comprising an AAV vector comprising a nucleic acid encoding NMDAR1 operably linked to a promoter and (ii) a method of ameliorating brain damage associated with epilepsy or stroke *in a rat,* via prior oral administration of said AAV vector…does not reasonably provide enablement for a composition comprising any vector encoding any NMDA receptor antigen, nor for a method of modulating or delaying onset of epilepsy, stroke, or decreased cognition *in any subject*, by administration of any vector encoding any NMDA receptor antigen."

The Examiner stated in the Office Action of June 11, 2009 that "the immune responses of rats to DNA vaccination correlates to the immune response of humans or other subjects."

The Examiner further cited the teachings of McCluskie et al. (McCluskie et al. (1999) Mol. Med. 5:287-300) to conclude that results obtained in a rat model of genetic immunization do not correlate with results obtained with other species. The Examiner stated in the Final Office

Action dated December 10, 2010 that McCluskie et al. teach that "the strength and nature of the immune responses to administration of DNA vaccines varies between species and that it is not clear that the results from one species are predictive in another (page 287, abstract)."

The Examiner further contended that oral administration is the only mode of administration that is enabled by the specification. Specifically, the Examiner states that "the availability of other modes of administration is not sufficient to enable the use of other modes of administration in the claimed invention because McCluskie amply demonstrates that different modes of administration produce varying effects that are not predictable."

The Examiner also argued that the specification only enables the use of AAV vectors. The Examiner states that "the availability of other vectors is not sufficient to enable the use of other vectors in the claimed methods because the art of record demonstrates that finding the appropriate vector, with the appropriate control sequences, under the appropriate mode of administration to provide a therapeutic effect, is unpredictable."

2. Claims 11-12 and 20-28 Are Enabled

Since composition claims 1-2 and 10 currently stand allowable, the scope of enablement is only pertinent to the pending method claims. Contrary to the assertions of the Examiner, the claims are enabled for one of ordinary skill in the art to make and use the invention.

"Subject"

The Examiner incorrectly rejected the claims by stating that there is no evidence that immune responses of rats to DNA vaccination correlate to the immune response of humans or other subjects. However, the specification, which presents experimental results in an animal model accepted by those skilled in the art, is enabling for a broader scope of *mammalian* subjects as defined in the specification, including humans. The acceptability of the rat model by those skilled in the art is demonstrated by the publication of the inventors' work in the peer-reviewed journal, *Science*, in 2000.

The publication, "An Oral Vaccine Against NMDAR-1 With Efficacy In Experimental Stroke And Epilepsy" Science vol. 287, pp 1453-1460 (2000) was submitted during prosecution

(Appellant's Response November 12, 2009) and is included in Appendix B.

The Examiner cited the McCluskie article as the principal basis for the enablement rejection, noting that:

> …McCluskie et al. teaches that the strength and nature of the immune responses to administration of DNA vaccines varies between species and that it is not clear that the results from one species are predictive in another (page 287, abstract).[1]

The suggestion that McCluskie's article makes the results "unpredictable" is not supported by the article. McCluskie investigated humoral responses to genetic vaccines in mice and monkeys and was able to detect immune responses in both species. However, the Examiner focuses on the difference in strength of immune responses demonstrated by the species as a grounds for unpredictability. McCluskie's experiments were designed such that a 10x difference in dosage was administered to the mice (0.1mg) and monkeys (1mg), while there is a 100x weight difference between the species. Thus, the mice were effectively given a 10x higher dosage of vaccine than the monkeys. So it is not at all surprising that the mice demonstrated robust antibody formation (having received 10x more DNA vaccine), and the monkeys demonstrated a weak antibody response. Given the results demonstrated by McCluskie, one of ordinary skill in the art would not arrive at the conclusion that immune responses between different species are unpredictable. In fact, the only conclusion one of ordinary skill in the art can properly draw from McCluskie is that DNA vaccine dosage may influence the strength of the immune response.

Moreover, Appellant points out that while the *strength* of the immune response may be varied in the data presented by McCluskie, an immune response was nonetheless present in both mice and monkeys. McCluskie even states in the last paragraph on page 296 that antibody efficacy "may be more related to dosage."

Evidence that the claimed invention produce an "ideal" response is also not required for enablement. Appellant has shown in the specification that DNA vaccination can elicit

[1] See page 4 of the December 10, 2009 Office Action.

production of NMDA receptor-1 antibodies, thereby producing an immune response in multiple models. An animal model is acceptable where it is recognized in the art that this model correlates to a specific condition. If this has not yet been established in the art, the animal model is acceptable if one skilled in the art would accept the model as *reasonably correlating* to the condition. This "reasonableness" standard serves to distinguish the enablement requirement of the patent laws from the more stringent standards of the FDA. Moreover, considerations made by the FDA for approving clinical trials are very different from those made by the PTO in determining whether a claim is enabled, *i.e.*, safety considerations are more properly left with the FDA. Scott v. Finney, 34 F.3d 1058, 1063 (Fed. Cir. 1994).

Furthermore, the standard stated in the MPEP 2164.02 is "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." The specification provides ample evidence to support the efficacy of the invention in an art recognized animal model. Administration of antigens elicited production of antibodies capable of crossing the blood-brain barrier to modify the function of the NMDA receptor.

The specification further supports efficacy of DNA vaccination to produce an immune response to ameliorate epilepsy or stroke in a mammalian subject as recited in claim 12. Example 3 of the specification describes the neuroprotective effect against epilepsy demonstrated in a well established and art recognized animal model for epilepsy. The specification also describes the anti-stroke and ischemic neuroprotection efficacy of the neuroprotective vaccine using an art recognized animal model for stroke (*See* Example 4).

"Administration"

The Examiner incorrectly rejected the claims by stating that oral administration is the only mode of administration that is enabled by the specification. While presenting experimental results with an *oral composition*, the specification also fully enables one of ordinary skill in the art to utilize other modes of administration. Furthermore, Appellant illustrates that usage of different modes of administration were well known and used in the art around and prior to the time of filing.

Contrary to the assertion of the Examiner, the specification is replete with teachings that enable one of ordinary skill in the art to utilize multiple modes of administration for DNA vaccination. For example, Section III of the specification, entitled "Pharmaceutical Compositions and Pharmaceutical administration" found in paragraphs [0120-0133] of the published application, and Section IV of the specification, entitled "Delivery Systems" found in paragraphs [0134-0148] of the published application, teach intravenous and intramuscular injection, respectively, as alternative delivery mechanisms.

Moreover, the McCluskie article actually supports enablement of Appellent's claims since multiple routes of DNA vaccination delivery were used in the McCluskie article to induce antibody production. The McCluskie article effectively demonstrates that prior to the invention various modes of genetic vaccine administration, such as intravenous injection, intramuscular, gene-gun and non-injected administration, were well known to one of ordinary skill in the art. The suggestion that McCluskie's article makes the claims "unpredictable" is not supported since McCluskie used varying modes of administration in different animal models and demonstrated antibody response to DNA vaccination.

It is well established that enablement is not precluded by the need for experimentation, even a large quantity of experimentation, if the specification, in combination with the knowledge available in the art, provides guidance regarding how to carry out the experimentation, such experimentation is not "undue." In re Wands, 858 F.2d 737, 742 (1988) (citing In re Angstadt, 537 F.2d 489, 502-504 (CCPA 1976)).

Furthermore,

> [t]he law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. *See Vivid Technologies, Inc. v. American Science and Engineering, Inc.* 200 F.3d 795, 804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999) ("Patents are written by and for the skilled artisans"). To hold otherwise would require every patent document to include a technical treatise for the unskilled reader. Although an accommodation to the "common experience" of lay persons may be feasible, it is an unnecessary burden for inventors and has long been rejected as a requirement for patent

> disclosures. *See Atmel Corp.*, 198 F.3d at 1382, 53 USPQ2d at 1230 (Fed. Cir. 1999) ("The specification would be of enormous and unnecessary length if one had to literally reinvent and described the wheel."); *W.L. Gore & Assoc., Inv. v. Farlock, Inc.*, 721 F.2d 1540, 1556, 220 U.S.P.Q. 303, 315 (Fed. Cir. 1983) ("Patents are written to enable those skilled in the art to practice the invention, no the public.").

S3 Inc. v. Nvidia Corp., 259 F.3d 1364, 1371 (Fed. Cir. 2001).

The working examples provided by the specification of the present invention are *merely illustrative* of the underlying inventive concept of Appellant's invention – they do *not* represent the sum total of Appellant's underlying inventive concept. Therefore, it is well within the capabilities of one of ordinary skill in the art, at the time of filing, to utilize the teachings of the specification, as well as the knowledge of the art, to administer a nucleic acid sequence antigen, via oral administration or the other recited modes, to produce antibodies in the circulatory system of a mammalian subject.

Appellant further submits that each of claims 24-28, which recite various specific modes of administration, are each independently patentable. The Examiner has not provided any specific reason why each of these modes would be unpredictable.

"Delivery Systems"

The Examiner also incorrectly rejected the claims by stating that the specification only enables the use of AAV vectors. However, the specification is replete with teachings and examples for use of different delivery systems. See, for example, Section IV, entitled "Delivery Systems" paragraphs [0135]-[0148], for discussion on the uses of different vectors. Based on these teachings, one of ordinary skill in the art would be capable of utilizing an array of vectors or delivery systems. In fact, as Appellant has stated previously, one of ordinary skill in the art having familiarity with AAV vectors, would have knowledge to make and use other vectors or delivery compositions.

Moreover, the Examiner supports the argument that the specification is only enabled for the use of AAV vectors by stating that "evoking an antibody response at any level, is not

sufficient to provide the biological effects recited in the claims." However, all the claims are directed to either a composition or a method that *elicits production of NMDA receptor-1 antibodies*, which has been constructively reduced to practice in the specification by describing the use of various vectors, as well as actually reduced to practice as shown in Examples 3 and 4.

Appellant further submits that each of claims 20-23, which recite various specific delivery systems, are each independently patentable. The Examiner has not provided any specific reason why each of these delivery systems would be unpredictable.

VIII. CONCLUSION

In summary, claims 11-12 and 20-28 are enables for mammalian subjects using various modes of administration and delivery systems. As stated above, the need for experimentation, even a large quantity of experimentation, does not preclude enablement, if the specification, in combination with the knowledge available in the art, provides guidance regarding how to carry out the experimentation. Therefore, knowledge at the time of the filing and teachings in the specification clearly provides sufficient support for one of ordinary skill in the art to make and use the entire scope of the invention, as claimed, without any undue experimentation.

Accordingly, Appellant respectfully requests the Board reconsider and reverse the Examiner's rejections of claims 11-12 and 20-28.

Respectfully submitted,

Dated: November 10, 2010 /Thomas J. Engellenner/

Thomas J. Engellenner
Reg. No. 28,711
Attorney for Appellant
NUTTER McCLENNEN & FISH LLP
Seaport West
155 Seaport Boulevard
Boston, MA 02210-2699
Telephone: (617) 439-2948
Facsimile : (617) 310-9948

APPENDIX A: CLAIMS ON APPEAL

1. (Previously Presented) A composition to inhibit N-methyl-D-aspartate activity comprising:

an adeno-associated virus vector comprising a nucleic acid sequence encoding for an N-methyl-D-aspartate (NMDA) receptor-1 antigen operably linked to a promoter and capable of being expressed in a subject to elicit production of NMDA receptor-1 antibodies that inhibit NMDA activity, and

a pharmaceutically-acceptable carrier.

2. (Previously Presented) The composition of claim 1, wherein the produced antibodies bind to an NMDA-1 receptor in the central nervous system.

3.-9. (Canceled)

10. (Previously Presented) The composition of claim 1, wherein the composition is a preparation for oral administration.

11. (Previously Presented) A method comprising the step of administering an adeno-associated viral (AAV) vector comprising a nucleic acid sequence encoding for an N-methyl-D-aspartate (NMDA) receptor-1 antigen operably linked to a promoter and capable of being expressed in a mammalian subject to elicit production of NMDA receptor-1 antibodies, and a pharmaceutically-acceptable carrier to a subject prior to a neuronal insult, whereby the produced NMDA receptor-1 antibodies are capable of passing across a blood-brain barrier into a central nervous system following the neuronal insult to inhibit NMDA activity.

12. (Previously Presented) A method comprising: administering a composition to a mammalian subject to inhibit N-methyl-D-aspartate activity comprising a composition comprising a nucleic acid sequence encoding for an N-methyl-D-aspartate (NMDA) receptor-1 antigen, and a pharmaceutically-acceptable carrier prior to a neuronal insult, wherein the antigen elicits the production of NMDA receptor-1 antibodies in a circulatory system of the subject

which bind to an NMDA receptor-1 in the central nervous system to ameliorate epilepsy or stroke in the mammalian subject.

13.-19. (Canceled)

20. (Previously Presented) The method of claim 12 wherein the method further comprises administering a vector comprising a nucleic acid sequence encoding for an N-methyl-D-aspartate (NMDA) receptor-1 antigen operably linked to a promoter and capable of being expressed in the subject.

21. (Previously Presented) The method of claim 20, wherein the vector is a viral vector.

22. (Previously Presented) The method of claim 21, wherein the viral vector is selected from the group consisting of an adeno-associated virus vector, an adenovirus vector, a herpes virus vector, a parvovirus vector, and a lentivirus vector.

23. (Previously Presented) The method of claim 22, wherein the viral vector is an adeno-associated virus vector.

24. (Previously Presented) The method of claim 12, wherein the composition further comprises a colloidal dispersion system.

25. (Previously Presented) The method of claim 12, wherein the composition further comprises an injectable particle coated with the nucleic acid sequence.

26. (Previously Presented) The method of claim 12, wherein the composition is a preparation for oral administration.

27. (Previously Presented) The method of claim 12, wherein the composition is a preparation for intravenous injection.

28. (Previously Presented) The method of claim 12, wherein the composition is a preparation for intramuscular injection.

APPENDIX B: EVIDENCE

During, "An Oral Vaccine Against NMDAR-1 With Efficacy In Experimental Stroke And Epilepsy" Science vol. 287, pp 1453-1460 (2000)

APPENDIX C: RELATED PROCEEDINGS

None.

1854892.1